REMARKS

In the Office action mailed on June 30, 2003, the claims were rejected under 35 U.S.C. § 102 and/or § 103 in view of Nova et al. and/or Pirrung et al. Applicants respectfully reserve the right to traverse all rejections in the previous Office action. However, for various reasons, and in order to advance prosecution of this application, applicants have elected to proceed with examination of a new set of claims directed to preferred examples of the invention. Accordingly, applicants have replaced the previously pending set of claims with a new set. As explained below, the new claims are fully supported by the original specification, and distinguishable from any of the art of record.

Request for Continued Examination

Applicants have submitted a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114. This request complies with the requirements of 37 C.F.R. § 1.114(a). In particular:

(i) Prosecution in the application is closed, since the last Office action was a final Office action under 37 C.F.R. § 1.113.

(ii) The Request is accompanied by a submission, specifically, the amendment to the claims set out above.

(iii) The Request is accompanied by the fee set forth at 37 C.F.R. § 1.17(e).

Accordingly, applicants respectfully request grant of their Request for Continued Examination.

Amendments

Claim 69 is directed to a system for conducting an experiment on biological cells. Support for the preamble can be found, for example, in Figure 7, and the corresponding description on page 18 of the specification.

Claim 69 recites a mixture of at least two carriers randomly distributed on the surface. Support for this can be found throughout the specification, for example, see Figure 4, and page 16, lines 30-32; Figure 7G, and description on page 18, lines 13 and 14; and page 26, lines 8-11.

Claim 69 also recites that the carriers have a flat surface. This element is supported in the specification on page 29, lines 21-23. The claim also recites that the carriers are formed of fused glass or plastic fibers of varying color. Support for these carrier limitations can be found, for example, beginning on page 12, line 32 through page 13, line 20.

Claim 69 also recites an imaging device which acquires a set of images, each image corresponding to a different spectral band. Support for this element can be found on page 21, lines 12-13.

Claim 69 also recites an image analysis system including a computer program to identify a class of cells supported by one or more carriers. Computers for analyzing and interpreting image information are shown in Figures 4 and 5. Image processing techniques employing appropriate software are described in the specification on pages 20 and 21. Details concerning development of and use of masks for one or more carriers of the same code are described on pages 6 and 7 of U.S. Provisional Patent Application

Serial No. 60/129,664, filed on April 15, 1999, which is incorporated by reference in the subject application. Portions of pages 6 and 7 from the provisional application are attached for the Examiner's convenience. The provisional application also refers to reference texts and commercially available software for use on a computer as recited in the claim.

New independent claim 80 is similar to previously examined claim 55 except that further explanation has been added to the claim relating to the structure of the carriers and use of fused glass fibers of various colors to form a detectable code. In the previous Office action, claim 55 was rejected as being anticipated by Pirrung et al. (U.S. Patent No. 5,143,854). Pirrung et al. fails to teach or suggest the recited carrier and code structures. Therefore, claims 80-86 are patentable over the art of record.

Applicants believe all of the pending claims are patentable over the art of record. Please contact applicants' attorney if there are any further issues to address.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being sent via first class mail in an envelope addressed to: BOX RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 on September 10, 2003.

Pamela A. Knight
Date of Signature: September 10, 2003

SUMMARY OF THE INVENTION

The described invention addresses the shortcomings of traditional two-dimensional microarrays. Firstly, by attaching the probe molecules to carriers one eliminates th use of printing robotics. Since all carriers of one class can be coated with a specific probe to analyte there is no need at all for printing in pre-determined coordinates. The identification of the different analytes is embedded in the recognition of the carrier class (e.g., by shape, size, color, code, etc.). An additional advantage of the invention is that after the different carriers are coated they can be mixed together and hybridized simultaneously in a small volume. This not only simplifies the process but also makes it inexpensive and more efficient. Finally the carriers can be deposited on a slide by a simple process (e.g., wedge smear, cytospin, gravity deposition).

The second shortcoming that this invention addresses is the standardization and reproducibility of microarray spots. As mentioned above, this is difficult to achieve in traditional printed arrays because of the source of the molecules (DNA can be viscous and therefore hard to deliver accurately) and the method of deposition (e.g., print head). This invention overcomes these obstacles by using pre-coated carriers. Once coated the carriers represent a homogenous source of molecules available for the reaction and for the accurate quantification. Furthermore, because they are pre-manufactured and pre-coated before the reaction, their production can be tightly controlled.

Due to its simplicity, this invention can be practiced by any laboratory without a major investment of time, labor and money. Reading of specimens produced according to the present invention can be done, for example, on a microscope equipped with appropriate optics, camera and software.

The method of identification of carriers depends on the nature of their properties. If carriers are beads of different size, the radius of beads can be estimated from the image of a field containing them in transmitted light, fluorescence, phase contrast or other microscope modalities. The most common way of acquiring a digital image at this time is by means of a CCD camera (ref. 30). Once the image of the field is obtained, it can be corrected for background variation. (ref. 31, 32), and thresholded (ref. 31, 32). Each connected set of pixels represents a bead. The area of such a set is the number of pixels, and from this area the radius can be calculated. This is the simplest way of estimating the radius. More accurate methods have been developed that give accuracy of a fraction of the pixel size (ref. 42, 43).

A high accuracy of measurement can be achieved by developing a theoretical model of image intensity distribution produced by each class of carriers and fitting it to the actually observed images.

$$\textit{Image Intensity} = f(x,y \mid P),$$

where: x, y are pixel coordinates relative to the center of the carrier, P is the parameter vector, which can consist, for example, of the size parameter and the brightness parameter.

Such functions can be constructed b cause th carrier classes, the microscope optics, and th image acquisition syst m are known and can b characterized analytically. The approximation of the theoretical imag int nsity to the observed image intensity can b done by the least squares method (ref. 44). The result of this approximation is a param ter vector, which gives the best fit. The values of parameters determine the class

to which the carrier belongs. In the example of beads of different sizes the accuracy of measurement and the accuracy of manufacturing of the beads determine the possible number of classes that can be allocated to the siz feature in a certain practical size range.

If carriers are different by color, a set of images, corresponding to different spectral bands, must be acquired. A combination of these images can be used to produce and analyze the mask of the beads as described in the previous paragraphs. For each bead mask relative image values can be determined in all spectral images. Each bead color will generate a characteristic set of these values, which can be used to identify them.

There are several commercially available image processing packages that could be used to perform all required operations for the described method (ref. 33, 34, 35, 36, 37, 38).

If the carriers are encoded chips one possible approach is pattern matching – a method commonly used in machine vision. Each code forms a pattern of dark and light squares and could be matched against each carrier, with the closest match giving the carrier class number. There are commercially available packages that implement this type of processing (ref. 38, 39, 40, 41). Alternatively, a specific algorithm can be developed to directly read the code from the carrier image. For example, such algorithm could comprise the following steps: correction for background non-uniformity, thresholding at a level that separates carriers from the background, filling the holes, approximation by a rectangle, rejection if the actual shape deviates from rectangular (the case of overlapping carriers), rotation to normalized orientation, measurement to average image value in the middle of subsquares, and generation of the code.

The preceding paragraphs dealt with image processing required to identify a carrier as belonging to a certain carrier class. The second task is to measure one or more reporting modalities, e.g., one or more fluorescent colors, or one or more absorptive colors (ref. 46) for each carrier. This can be done essentially with the same image processing methods, e.g., correcting the background and calculating the integrated intensity within the carrier mask.